

disorders, the effectiveness of treating IPV with SEPS has been maddeningly difficult to prove.

**Treatment of Proximal Deep-Vein Thrombosis with the Oral Direct Factor Xa Inhibitor Rivaroxaban (BAY 59-7939): The ODIx-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients with Acute Symptomatic Deep-Vein Thrombosis) Study**

Agnelli G, Gallus A, Goldhaber SZ, and the ODIx-DVT Study Investigators. *Circulation* 2007;116:180-7.

**Conclusion:** The orally active direct factor Xa inhibitor rivaroxaban appears effective in treatment of proximal deep-vein thrombosis (DVT).

**Summary:** There is a major need for an orally active anticoagulant that does not require long-term monitoring or dose adjustment. A potential anticoagulant meeting those requirements is rivaroxaban (BAY 59-7939). This is an oral direct factor Xa inhibitor currently under clinical development. This study was a parallel-group, randomized, dose-ranging, phase II trial in patients with proximal DVT. The study was designed to evaluate the safety and efficacy of BAY 59-7939, using doses of 10, 20, or 30 mg twice daily (BID) or 40 mg once daily compared with enoxaparin, 1 mg/kg BID, followed by a vitamin K antagonist. Treatments were administered for 12 weeks. The primary end point was "improvement in thrombotic burden" at 3 weeks. This was assessed by quantitative compression duplex ultrasonography and defined as  $\geq 4$ -point improvement in a thrombus score without recurrent symptomatic DVT or a DVT-related death.

The primary efficacy end point was achieved in 53% (53 in 100) patients treated with 10 mg of rivaroxaban. Primary efficacy end points were also achieved in 59.2% (58 of 98), 56.9% (69 of 109), and 43.8% (49 of 112) patients receiving 20 or 30 mg BID or 40 mg once daily of rivaroxaban. In the 109 patients treated with enoxaparin and a vitamin K antagonist, the primary end point was achieved in 45.9% (50 of 109) patients. There was no significant trend in the dose-response relationship between the primary efficacy end point and rivaroxaban BID ( $P = .67$ ). In the patients receiving 10 or 20 mg of rivaroxaban BID or 40 mg once daily, major bleeding was observed in 1.7%. In the patients receiving 30 mg BID of rivaroxaban, major bleeding occurred in 3.3%. There were no major bleeding events with an enoxaparin and vitamin K antagonist.

**Comment:** This was essentially a phase II proof-of-concept trial of a new oral anticoagulant. Clearly, a safe orally administered anticoagulant that requires no monitoring would be a major step forward. The data justified performance of a larger phase III evaluation. Although the mechanism of action of rivaroxaban is different than ximelagatran, the hepatic toxicity associated with ximelagatran (Drug Safety 2005;28:351-70) mandates intense surveillance for liver toxicity in a phase III study of rivaroxaban.

**Effect of Perindopril on Large Artery Stiffness and Aortic Root Diameter in Patients with Marfan Syndrome: A Randomized Controlled Trial**

Ahimastos A, Aggarwal A, D'Orsa K, et al. *JAMA* 2007;298:1539-47.

**Conclusion:** Perindopril reduces aortic stiffness and aortic root diameter in patients with Marfan syndrome taking standard  $\beta$ -blocker therapy.

**Summary:** Angiotensin-converting enzymes (ACE) can reduce arterial stiffness. Aortic stiffness is increased in Marfan syndrome and contributes to aortic dilatation and rupture. Traditionally, patients with Marfan syndrome are treated with  $\beta$ -blocker therapy. It is thought  $\beta$ -blockers induce reduction in pressure change in the aortic root, thereby decreasing aortic wall stress. The rennin-angiotensin system may lead to development of aortic stiffening and is perhaps a more direct underlying pathophysiologic mechanism that results in aortic dilatation and rupture in patients with Marfan syndrome.

The authors performed a double blind, randomized, placebo-controlled trial of 17 patients with Marfan syndrome. The patients were aged  $33 \pm 6$  years and were on standard  $\beta$ -blocker therapy. The trial was initiated in January 2004 and completed in September 2006. Patients were administered 8 mg/d of perindopril ( $n = 10$ ) or placebo ( $n = 7$ ) for 24 weeks. Central and peripheral pulse wave velocities and systemic compliance were used to measure arterial stiffness. Aortic root diameter was assessed with transthoracic echocardiography.

Central arterial stiffness (increased systemic arterial compliance) was decreased at 24 weeks in the perindopril group vs the placebo group ( $P = .004$ ). Arterial stiffness was also reduced peripherally as measured by increased arterial compliance in the perindopril group vs placebo ( $P < .001$ ). Perindopril also reduced aortic root diameters relative to placebo in both end-systole and end-diastole ( $P < .01$  to  $P < .001$  for all comparisons between groups). Transforming growth factor- $\beta$  (TGF- $\beta$ ), a contributor to aortic degeneration in Marfan syndrome, was reduced by perindopril compared with placebo ( $P < .01$ ).

**Comment:** Data indicate that adjunct therapy using ACE inhibitors in addition to  $\beta$ -blockers reduces arterial stiffness and aortic root diameters in patients with Marfan syndrome. The observed reduction in TGF- $\beta$  likely

occurs through reduced signaling of the angiotensin II type 1 and angiotensin II type 2 receptors. The study is limited by small sample size and short duration. The findings are, however, sufficiently dramatic, and will likely rapidly influence basic medical management of patients with Marfan syndrome.

**Patent Foramen Ovale and Cryptogenic Stroke in Older Patients**

Handke M, Harloff A, Olschewski M, et al. *N Engl J Med* 2007;357:2262-8.

**Conclusion:** Paradoxical embolism is a cause of stroke both in patients aged  $<55$  and  $>55$  years.

**Summary:** Routine diagnostic testing fails to diagnose the cause of stroke in about 40% of patients (Ann Neuro 1989;25:382-90). The foramen ovale remains patent in about one-fourth of the overall population. It may facilitate stroke through paradoxical embolism. There is a known association between cryptogenic stroke and a patent foramen ovale in patients aged  $<55$  years. This study sought to determine whether there was such an association in patients aged  $>55$  years.

There were 503 consecutive patients with stroke who were prospectively examined. Of these, 276 served as control patients, in that they had a known cause of stroke, and 227 patients had an unknown cause of stroke, or cryptogenic stroke. The prevalence of a patent foramen ovale and patent foramen ovale with concomitant atrial septal aneurysm, as determined by transesophageal echocardiography (TEE), was examined. The authors also examined data comparing 131 patients aged  $<55$  years with 372 patients aged  $>55$  years.

Compared with patients with stroke of known cause, the prevalence of a patent foramen ovale was greater in those with cryptogenic stroke in both younger patients (43.9% vs 14.3%; odds ratio [OR], 4.70; 95% confidence interval [CI], 1.89-11.68;  $P < .001$ ) and older patients (28.3% vs 11.9%; OR, 2.92; 95% CI, 1.70-5.01;  $P < .001$ ). Cryptogenic stroke was even more strongly associated with the presence of a patent foramen ovale with concomitant atrial septal aneurysm compared with those patients with stroke of known cause. This was true among both younger patients (13.4% vs 2.0%; OR, 7.36; 95% CI, 1.01-326.6;  $P = .049$ ) and older patients (15.2% vs 4.4%; OR, 3.88; 95% CI, 1.78-8.46;  $P < .001$ ). Adjusting for plaque thickness, coronary disease, age, and hypertension, the presence of a patent foramen ovale was independently associated with cryptogenic stroke in both the older patient group (OR, 3.00; 95% CI, 1.73-5.23;  $P < .001$ ) and the younger patient group (OR, 3.70; 95% CI, 1.42-9.65;  $P = .008$ ).

**Comment:** The presence of patent foramen ovale decreases with increasing age (Mayo Clin Proc 1984;59:17-20). Nevertheless, the data indicate that a patent foramen ovale, especially with concomitant atrial septal aneurysm, places patients at significant risk for stroke. Although current data indicate this risk, they do not provide recommendations for treatment. Currently, however, there are several ongoing randomized trials to determine appropriate therapy for patients with a patent foramen ovale. Evidence-based treatment recommendations should therefore be available reasonably soon.

**Therapeutic Benefit of Low-Dose Clopidogrel in Patients Undergoing Carotid Surgery Is Linked to Variability in the Platelet Adenosine Diphosphate Response and Patients' Weight**

Payne DA, Jones CI, Hayes PD, et al. *Stroke* 2007;38:2464-9.

**Conclusion:** The ability of one 75-mg dose of clopidogrel to reduce transcranial Doppler (TCD)-detected embolization after carotid endarterectomy (CEA) is achieved by clopidogrel-induced prevention of monocyte-platelet aggregates.

**Summary:** The authors have previously shown that a single 75-mg dose of clopidogrel can reduce TCD-detected embolization after CEA (Circulation 2004;109:1476-81). It is, however, known that dosing of clopidogrel at 75 mg/d produces only incremental effects in reducing adenosine diphosphate (ADP)-mediated platelet activation, with maximum reduction not occurring until after 7 days. This is contrast to the ability of a 300- to 600-mg loading dose of clopidogrel to produce rapid and pronounced platelet inhibitory effects (Semin Thromb Hemost 1999; 25 [suppl 2]: 15-19).

In this article, the authors sought to explain the mechanism of how a single dose of clopidogrel reduces TCD-detected embolic events after CEA. The study randomized 56 patients on long-term aspirin therapy (150 mg/d) to 75 mg of clopidogrel or placebo before CEA. Platelet activation and ADP responses, determined by flow cytometry and aggregometry, were measured before and after drug administration and at the end of surgery. There was a significant surgery-induced rise in platelet activation in vivo. There was a rise in the percentage of monocyte-platelet aggregates in patients given placebo that was not seen in patients receiving clopidogrel. Platelet response was more pronounced after surgery, and clopidogrel produced a significant reduction in platelet